



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 11/1/2012 EST.

Visit the AIDSinfo website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

# Adherence to Antiretroviral Therapy in HIV-Infected Children and Adolescents (Updated August 11, 2011)

## Panel's Recommendations

- Strategies to maximize adherence should be discussed before initiation of antiretroviral therapy (ART) and again prior to changing regimens **(AIII)**.
- Adherence to therapy must be stressed at each visit, along with continued exploration of strategies to maintain and/or improve adherence **(AIII)**.
- At least one method of measuring adherence to ART (e.g., quantitative and/or qualitative self-report, pharmacy refill checks, pill counts) should be used in addition to monitoring viral load **(AII)**.
- When feasible, once-daily antiretroviral (ARV) regimens should be prescribed **(AI\*)**.
- To improve and support adherence, providers should maintain a nonjudgmental attitude, establish trust with the patient/caregiver, and identify mutually acceptable goals for care **(AII\*)**.

## Background

Medication adherence is fundamental to successful ART. Adherence is a major factor in determining the degree of viral suppression achieved in response to ART<sup>1-4</sup>. Poor adherence can lead to virologic failure. Prospective adult and pediatric studies have shown the risk of virologic failure to increase as the proportion of missed doses increases<sup>2, 5-6</sup>. Based on early work in populations of adults primarily being treated with nonboosted protease inhibitor (PI)-based regimens<sup>2</sup>, 95% adherence has been the threshold associated with complete viral suppression. Recent findings from adult populations suggest that the relationship between ARV adherence and viral suppression may vary with individual drug and drug class as well as pattern of adherence<sup>7</sup>. Viral suppression can be achieved with lower levels of adherence when using boosted PI and non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens<sup>7-9</sup>. Different patterns of inadequate adherence (intermittent missed doses, treatment interruptions) may have a differential impact on regimen efficacy depending on the drug combination<sup>10</sup>.

Subtherapeutic ARV drug levels resulting from poor adherence may facilitate the development of drug resistance to one or more drugs in a given regimen and possible cross resistance to other drugs in the same class. Multiple factors, including regimen potency, pharmacokinetics (PKs), viral fitness, and the genetic barrier to ARV resistance, influence the adherence-resistance relationship<sup>11</sup>. In addition to compromising the efficacy of the current regimen, suboptimal adherence has implications for limiting future effective drug regimens for patients who develop drug-resistant viral strains.

Evidence indicates that adherence problems occur frequently in children and adolescents. Multiple studies have reported that fewer than 50% of children and/or caretakers reported full adherence to prescribed regimens. Rates of adherence varied with method of ascertainment (parent/child report, pharmacy records), ARV regimens, and study characteristics<sup>3-4, 12-17</sup>. A variety of factors, including medication formulation, frequency of dosing, child age, and psychosocial characteristics of the child and parent, have been associated with adherence; however, no clear predictors of either good or poor adherence in children have been consistently identified<sup>12, 14, 18-23</sup>. Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment<sup>6, 24</sup>. These findings illustrate the difficulty of

maintaining high levels of adherence and underscore the need to work in partnership with families to make adherence education, support, and assessment integral components of care.

## Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by the regimen prescribed, patient and family factors, and characteristics of health care providers<sup>21-22</sup>. Limited availability of palatable formulations for young children is especially problematic<sup>5, 25</sup>. Furthermore, infants and children are dependent on others for administration of medication; thus, assessment of the capacity for adherence to a complex multidrug regimen requires evaluation of the caregivers and their environments as well as the ability and willingness of the child to take the drug. Barriers faced by adult caregivers that can contribute to nonadherence in children include forgetting doses, changes in routine, being too busy, and child refusal of medications<sup>26</sup>. Some caregivers may place too much responsibility for managing medications on older children before the children are developmentally able to take on such tasks<sup>27</sup>. Many other barriers to adherence exist for children with HIV infection. For example, caregivers' unwillingness to disclose the child's HIV infection status to others may create specific problems, including reluctance of caregivers to fill prescriptions locally, hiding or relabeling of medications to maintain secrecy within the household, avoidance of social support, and a tendency for doses to be missed if the parent is unavailable.

## Specific Adherence Issues for Adolescents

HIV-infected adolescents also face specific adherence challenges<sup>18, 28-30</sup>. Several studies have identified pill burden as well as lifestyle issues (i.e., not having medications on hand when away from home, change in schedule) as barriers to complete adherence<sup>18, 28</sup>. Adolescents' denial and fear of their HIV infection is common, especially in recently diagnosed youth; this may lead to refusal to initiate or continue ART. Distrust of the medical establishment, misinformation about HIV, and lack of knowledge about the availability and effectiveness of ARV treatments can all be barriers to linking adolescents to care and maintaining successful ART. Perinatally infected youth are familiar with the challenges of taking complex drug regimens and with the routine of chronic medical care; nevertheless, they may have long histories of inadequate adherence. Regimen fatigue has also been identified as a barrier to adherence in adolescents<sup>31</sup>. Regardless of the mode of acquisition of HIV infection, HIV-infected adolescents may suffer from low self-esteem, may have unstructured and chaotic lifestyles and concomitant mental illnesses, or may cope poorly with their illness because they lack familial and social support. Depression, alcohol or substance abuse, poor school attendance, and advanced HIV disease stage all correlate with nonadherence<sup>29, 32</sup>. In a study of 833 HIV-infected Medicaid beneficiaries 12–17 years of age, youth diagnosed with a psychiatric comorbidity (substance abuse, conduct disorder, or emotional disorder) were less likely to be receiving combination therapy; however, for those on therapy, only a conduct disorder diagnosis was associated with poorer adherence<sup>33</sup>. In a cross-sectional study of youth with perinatal HIV infection, no significant differences in the frequency of mental health disorders were found between adherent and nonadherent participants<sup>34</sup>. A review of published papers on adherence among HIV-infected youth, however, suggests that depression and anxiety have been consistently associated with poorer adherence<sup>32</sup>. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Further difficulties face adolescents who live with parents or partners to whom they have not yet disclosed their HIV status and adolescents who are homeless and have no place to store medicine. When recommending treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ARV regimen with realistic assessment of existing and potential support systems to facilitate adherence.

Interventions to promote long-term adherence to ARV treatment have not been rigorously evaluated in adolescents. In clinical practice, reminder systems, such as beepers and alarm devices, are well accepted by some youth. Small, inconspicuous pillboxes may be useful for storing medications in an organized fashion. In a pilot study evaluating peer support and pager messaging in an adult population, peer support was associated with greater self-reported adherence post-intervention; however, the effect was not sustained at follow-up. Although pager messaging was not associated with reported adherence, improved biologic outcomes were measured<sup>35</sup>. Another study evaluating the efficacy of a four-session, individual, clinic-based motivational interviewing intervention targeting multiple risk behaviors in HIV-infected youth demonstrated an association with lower viral load at 6 months among youth taking ART. However, reduction in viral load was not maintained at 9 months<sup>36</sup>.

## Adherence Assessment and Monitoring

The process of adherence preparation and assessment should begin before therapy is initiated or changed. A routine adherence assessment should be incorporated into every clinic visit. A comprehensive assessment should be instituted for all children in whom ARV treatment initiation or change is considered. Evaluations should include nursing, social, and behavioral assessments of factors that may affect adherence by the child and family and can be used to identify individual needs for intervention. Adherence preparation should focus on establishing a dialogue and a partnership with the child and family regarding medication management. Specific, open-ended questions should be used to elicit information about past experience as well as concerns and expectations about treatment. When assessing readiness and preparing to begin treatment, it is important to obtain the patient's explicit agreement with the treatment plan, including strategies to support adherence. Also, it is important to alert patients to the minor side effects of ARV drugs, such as nausea, headaches, and abdominal discomfort, that may recede over time or respond to change in diet or method and timing of medication administration.

Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations<sup>17, 37-39</sup>. Both caregivers and health care providers often overestimate adherence. Use of multiple methods to assess adherence is recommended. Viral load response to a new regimen is often the most accurate indication of adherence, but it may be a less valuable measure in children with long treatment histories and multidrug-resistant virus. Other measures include quantitative self-report of missed doses by caregivers and children or adolescents (focusing on recent missed doses during a 3-day or 1-week period), descriptions of the medication regimens, and reports of barriers to administration of medications. Caregivers may report number of doses taken more accurately than doses missed<sup>40</sup>. Also, targeted questions about stress, pill burden, and daily routine are recommended<sup>12, 18, 37</sup>. Pharmacy refill checks and pill counts can identify adherence problems not evident from self-reports<sup>41</sup>. Electronic monitoring devices, such as Medication Event Monitoring System (MEMS) caps, which are equipped with a computer chip that records each opening of a medication bottle<sup>42</sup>, have been shown to be useful tools to measure adherence in some settings<sup>41, 43-44</sup>. Home visits can play an important role in assessing adherence. In some cases, suspected nonadherence is confirmed only when dramatic clinical responses to ART occur during hospitalizations or in other supervised settings<sup>45-46</sup>. Preliminary studies suggest that monitoring plasma concentrations of PIs, or therapeutic drug monitoring (TDM), may be a useful method to identify nonadherence<sup>47</sup>.

It is important for clinicians to recognize that nonadherence is a common problem and that it can be difficult for patients to share information about missed doses or difficulties adhering to treatment. Furthermore, adherence can change over time. An adolescent who was able to strictly adhere to treatment upon initiation of a regimen may not be able to maintain complete adherence over time. A nonjudgmental atti-

tude and trusting relationship foster open communication and facilitate assessment. To obtain information on adherence in older children, it is often helpful to ask both the HIV-infected child and caregivers about missed doses and problems. Their reports may differ significantly; therefore, clinical judgment is required to best interpret adherence information obtained from the multiple sources<sup>48-49</sup>.

## Strategies to Improve and Support Adherence

Intensive follow-up is required, particularly during the critical first few months after therapy is started. Patients should be seen frequently, **as often as weekly during the first month of treatment**, to assess adherence and determine the need for strategies to improve and support adherence. Strategies include development of patient-focused treatment plans to accommodate specific patient needs, integration of medication administration into the daily routines of life (e.g., associating medication administration with daily activities such as brushing teeth), and use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers rather than one specific intervention may be most effective<sup>27, 50-53</sup>. Programs designed for administration of directly observed combination therapy to adults in either the clinic or at home have demonstrated successful results in both the United States and in international, resource-poor settings<sup>54-58</sup>. **Modified directly observed therapy (m-DOT), where one dose is administered in a supervised setting and the remaining doses are self-administered, appears to be both feasible and acceptable<sup>53</sup>. However, a recent meta-analysis of 10 randomized clinical trials evaluating DOT to promote adherence in adults found that DOT was no more effective than self-administered treatment<sup>59</sup>. In another meta-analysis of DOT studies, DOT was found to have a demonstrated effect on virologic, immunologic, and adherence outcomes, but efficacy of the strategy was not supported when the analysis was restricted to randomized controlled trials<sup>60</sup>.** [Table 16](#) summarizes some of the strategies that can be used to support and improve adherence to ARV medications.

### *Regimen-Related Strategies*

Highly active ARV regimens often require the administration of large numbers of pills or unpalatable liquids, each with potential side effects and drug interactions, in multiple daily doses. To the extent possible, regimens should be simplified with respect to the number of pills or volume of liquid prescribed, as well as frequency of therapy, and chosen to minimize drug interactions and side effects<sup>61</sup>. When non-adherence is a problem, addressing medication-related issues, such as side effects, may result in improvement. If a regimen is overly complex, it may be simplified. For example, when the burden of pills is great, one or more drugs can be changed to result in a regimen containing fewer pills and potentially greater adherence. **When feasible, once-daily regimens should be prescribed.** Several studies in adults have demonstrated better adherence in once-daily compared with twice-daily ARV regimens<sup>62-65</sup>. When nonadherence is related to poor palatability of a liquid formulation or crushed pills and simultaneous administration of food is not contraindicated, the offending taste may be masked by a small amount of flavoring syrups or food (see [Appendix A: Pediatric Antiretroviral Drug Information](#)) or the child may be taught to swallow pills in order to overcome medication aversion<sup>66</sup>.

### *Child/Family-Related Strategies*

The primary approach taken by the clinical team to promote medication adherence in children is patient/caregiver education. Educating families about adherence should begin before ARV medications are initiated or changed and should include a discussion of the goals of therapy, the reasons for making adherence a priority, and the specific plans for supporting and maintaining the child's medication adherence. Caregivers should understand that the first ARV regimen has the best chance of long-term success.



Caregiver adherence education strategies should include the provision of both information and adherence tools, such as written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pillboxes.

A number of behavioral tools can be used to integrate taking medications into the HIV-infected child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives for taking medications, can be effective tools to promote adherence<sup>67-68</sup>. Training children to swallow pills has been associated with improved adherence at 6 months post-training in a small study of children 4 to 21 years of age<sup>69</sup>. Availability of mental health services and treatment of mental health disorders may also facilitate adherence to complex ARV regimens. For nonadherent children who are at risk of disease progression and for whom aversion to taking medications is severe and persistent, a gastrostomy tube may be considered<sup>70</sup>. If adequate resources are available, home nursing interventions may also be beneficial<sup>71</sup>. Directly observed dosing of ARV medications has been implemented in adults, adolescents, and children<sup>59-60, 72</sup>, using home nursing services as well as daily medication administration in the clinic setting. Other strategies to support adherence that have been employed in the clinical setting include setting patients' cell phone alarms to go off at medication times; providing pill boxes and other adherence support tools; weekly filling of pill boxes by nursing or pharmacy staff, particularly for patients with complex regimens; and home delivery of medications.

### ***Health Care Provider-Related Strategies***

Providers have the ability to improve adherence through their relationships with the families. This process begins early in the provider's relationship with the family, when the clinician obtains explicit agreement about the medication and treatment plan and any further strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important<sup>73-75</sup>. Provider characteristics that have been associated with improved patient adherence in adults include consistency, giving information, asking questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child centered and includes caregivers in adherence support has also been shown to improve treatment outcomes<sup>76</sup>.

**Table 16. Strategies to Improve Adherence to Antiretroviral Medications**

<b>Initial Intervention Strategies</b>
<ul style="list-style-type: none"><li>• Establish trust and identify mutually acceptable goals for care with patient and caregiver.</li><li>• Obtain explicit agreement on need for treatment and adherence with patient and caregiver.</li><li>• Identify depression, low self-esteem, substance abuse, or other mental health issues for the child/adolescent and/or caregiver that may decrease adherence. Treat mental health issues prior to starting antiretroviral (ARV) drugs, if possible.</li><li>• Identify family, friends, health team members, or others who can support adherence.</li><li>• Educate patient and family about the critical role of adherence in therapy outcome.</li><li>• Specify the adherence target: <math>\geq 95\%</math> of prescribed doses.</li><li>• Educate patient and family about the relationship between partial adherence and resistance.</li><li>• Educate patient and family about resistance and constraint of later choices of ARV drug (i.e., explain that although a failure of adherence may be temporary, the effects on treatment choice may be permanent).</li><li>• Develop a treatment plan that the patient and family understand and to which they feel committed.</li><li>• Establish readiness to take medication by practice sessions or other means.</li><li>• Consider a brief period of hospitalization at start of therapy in selected circumstances for patient education and to assess tolerability of medications chosen.</li></ul>
<b>Medication Strategies</b>
<ul style="list-style-type: none"><li>• Choose the simplest regimen possible, reducing dosing frequency and number of pills.</li><li>• Choose a regimen with dosing requirements that best conform to the daily and weekly routines and variations in patient and family activities.</li><li>• Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to increase palatability).</li><li>• Choose drugs with the fewest side effects; provide anticipatory guidance for management of side effects.</li><li>• Simplify food requirements for medication administration.</li><li>• Prescribe drugs carefully to avoid adverse drug-drug interactions.</li><li>• Assess pill-swallowing capacity and offer pill-swallowing training.</li></ul>
<b>Follow-up Intervention Strategies</b>
<ul style="list-style-type: none"><li>• Monitor adherence at each visit and in between visits by telephone or letter as needed.</li><li>• Provide ongoing support, encouragement, and understanding of the difficulties associated with demands to attain 95% adherence with medication doses.</li><li>• Use patient education aids including pictures, calendars, and stickers.</li><li>• Encourage use of pill boxes, reminders, alarms, pagers, and timers.</li><li>• Provide follow-up clinic visits or telephone calls to support and assess adherence.</li><li>• Provide access to support groups, peer groups, or one-on-one counseling for caregivers and patients, especially for those with known depression or drug use issues that are known to decrease adherence.</li><li>• Provide pharmacist-based adherence support such as medication education and counseling, refill reminders, and home delivery of medications.</li><li>• Consider gastrostomy tube use in selected circumstances.</li><li>• Consider directly observed therapy (DOT) at home, in the clinic, or during a brief inpatient hospitalization.</li></ul>

## References

1. Flynn PM, Rudy BJ, Douglas SD, et al. Virologic and immunologic outcomes after 24 weeks in HIV type 1-infected adolescents receiving highly active antiretroviral therapy. *J Infect Dis*. 2004;190(2):271-279.
2. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133(1):21-30.
3. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics*. 2002;109(4):e61.
4. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 1999;18(8):682-689.
5. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J*. 2005;24(9):793-800.
6. Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. *AIDS*. 2002;16(16):2175-2182.
7. Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. *Curr HIV/AIDS Rep*. 2007;4(2):65-72.
8. Shuter J, Sarlo JA, Kanmaz TJ, et al. HIV-infected patients receiving lopinavir/ritonavir-based antiretroviral therapy achieve high rates of virologic suppression despite adherence rates less than 95%. *J Acquir Immune Defic Syndr*. 2007;45(1):4-8.
9. Nelson M, Girard PM, Demasi R, et al. Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naïve, HIV-infected patients: 96 week ARTEMIS data. *J Antimicrob Chemother*. 2010;65(7):1505-1509.
10. Parienti JJ, Ragland K, Lucht F, et al. Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. *Clin Infect Dis*. 2010;50(8):1192-1197.
11. Gardner EM, Burman WJ, Steiner JF, et al. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS*. 2009;23(9):1035-1046.
12. French T, Weiss L, Waters M, et al. Correlation of a brief perceived stress measure with nonadherence to antiretroviral therapy over time. *J Acquir Immune Defic Syndr*. 2005;38(5):590-597.
13. Katko E, Johnson GM, Fowler SL, et al. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2001;20(12):1174-1176.
14. Mellins CA, Brackis-Cott E, Dolezal C, et al. The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2004;23(11):1035-1041.
15. Reddington C, Cohen J, Baldillo A, et al. Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2000;19(12):1148-1153.
16. Ding H, Wilson CM, Modjarrad K, et al. Predictors of suboptimal virologic response to highly active antiretroviral therapy among human immunodeficiency virus-infected adolescents: analyses of the reaching for excellence in adolescent care and health (REACH) project. *Arch Pediatr Adolesc Med*. 2009;163(12):1100-1105.
17. Khan M, Song X, Williams K, et al. Evaluating adherence to medication in children and adolescents with HIV. *Arch Dis Child*. 2009;94(12):970-973.
18. Murphy DA, Sarr M, Durako SJ, et al. Barriers to HAART adherence among human immunodeficiency virus-infected adolescents. *Arch Pediatr Adolesc Med*. 2003;157(3):249-255.



19. Williams PL, Storm D, Montepiedra G, et al. Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics*. 2006;118(6):e1745-1757.
20. Malee K, Williams PL, Montepiedra G, et al. The role of cognitive functioning in medication adherence of children and adolescents with HIV infection. *J Pediatr Psychol*. 2009;34(2):164-175.
21. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep*. 2009;6(4):194-200.
22. Marón G, Herr M, Gaur A, et al. Adherence rates in adolescents prescribed once daily and twice daily doses of highly active antiretroviral therapy (HAART). Paper presented at: St. Jude/PIDS Research Conference; 2008; Memphis, TN.
23. Filho LF, Nogueira SA, Machado ES, et al. Factors associated with lack of antiretroviral adherence among adolescents in a reference centre in Rio de Janeiro, Brazil. *Int J STD AIDS*. 2008;19(10):685-688.
24. Giannattasio A, Albano F, Giacommet V, et al. The changing pattern of adherence to antiretroviral therapy assessed at two time points, 12 months apart, in a cohort of HIV-infected children. *Expert Opin Pharmacother*. 2009;10(17):2773-2778.
25. Gibb DM, Goodall RL, Giacommet V, et al. Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. *Pediatr Infect Dis J*. 2003;22(1):56-62.
26. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS*. 2008;22(8):637-647.
27. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol*. 2009;34(2):187-194.
28. Belzer ME, Fuchs DN, Luftman GS, et al. Antiretroviral adherence issues among HIV-positive adolescents and young adults. *J Adolesc Health*. 1999;25(5):316-319.
29. Murphy DA, Belzer M, Durako SJ, et al. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. *Arch Pediatr Adolesc Med*. 2005;159(8):764-770.
30. Rudy BJ, Murphy DA, Harris DR, et al. Patient-related risks for nonadherence to antiretroviral therapy among HIV-infected youth in the United States: a study of prevalence and interactions. *AIDS Patient Care STDS*. 2009;23(3):185-194.
31. Merzel C, Vandevanter N, Irvine M. Adherence to antiretroviral therapy among older children and adolescents with HIV: a qualitative study of psychosocial contexts. *AIDS Patient Care STDS*. 2008;22(12):977-987.
32. Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med*. 2009;17(1):14-25.
33. Walkup J, Akincigil A, Bilder S, et al. Psychiatric diagnosis and antiretroviral adherence among adolescent Medicaid beneficiaries diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome. *J Nerv Ment Dis*. 2009;197(5):354-361.
34. Rudy BJ, Murphy DA, Harris DR, et al. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. *AIDS Patient Care STDS*. 2010;24(2):97-104.
35. Simoni JM, Huh D, Frick PA, et al. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2009;52(4):465-473.
36. Naar-King S, Parsons JT, Murphy DA, et al. Improving health outcomes for youth living with the human immunodeficiency virus: a multisite randomized trial of a motivational intervention targeting multiple risk behaviors. *Arch Pediatr Adolesc Med*. 2009;163(12):1092-1098.
37. Wiener L, Riekert K, Ryder C, et al. Assessing medication adherence in adolescents with HIV when electronic monitoring is not feasible. *AIDS Patient Care STDS*. 2004;18(9):527-538.
38. Davies MA, Boule A, Fakir T, et al. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. *BMC Pediatr*. 2008;8:34.

39. Farley JJ, Montepiedra G, Storm D, et al. Assessment of adherence to antiretroviral therapy in perinatally HIV-infected children and youth using self-report measures and pill count. *J Dev Behav Pediatr*. 2008;29(5):377-384.
40. Allison SM, Koenig LJ, Marhefka SL, et al. Assessing medication adherence of perinatally HIV-infected children using caregiver interviews. *J Assoc Nurses AIDS Care*. 2010;21(6):478-488.
41. Farley J, Hines S, Musk A, et al. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. *J Acquir Immune Defic Syndr*. 2003;33(2):211-218.
42. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. *Am J Hosp Pharm*. 1991;48(9):1978-1988.
43. Bova CA, Fennie KP, Knafl GJ, et al. Use of electronic monitoring devices to measure antiretroviral adherence: practical considerations. *AIDS Behav*. 2005;9(1):103-110.
44. Muller AD, Bode S, Myer L, et al. Electronic measurement of adherence to pediatric antiretroviral therapy in South Africa. *Pediatr Infect Dis J*. 2008;27(3):257-262.
45. Parsons GN, Siberry GK, Parsons JK, et al. Multidisciplinary, inpatient directly observed therapy for HIV-1-infected children and adolescents failing HAART: A retrospective study. *AIDS Patient Care STDS*. 2006;20(4):275-284.
46. Glikman D, Walsh L, Valkenburg J, et al. Hospital-based directly observed therapy for HIV-infected children and adolescents to assess adherence to antiretroviral medications. *Pediatrics*. 2007;119(5):e1142-1148.
47. van Rossum AM, Bergshoeff AS, Fraaij PL, et al. Therapeutic drug monitoring of indinavir and nelfinavir to assess adherence to therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 2002;21(8):743-747.
48. Dolezal C, Mellins C, Brackis-Cott E, et al. The reliability of reports of medical adherence from children with HIV and their adult caregivers. *J Pediatr Psychol*. 2003;28(5):355-361.
49. Podsadecki TJ, Vrijens BC, Tousset EP, et al. "White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients. *HIV Clin Trials*. 2008;9(4):238-246.
50. Haynes RB, McKibbin KA, Kanani R. Systematic review of randomised trials of interventions to assist patients to follow prescriptions for medications. *Lancet*. 1996;348(9024):383-386.
51. Winnick S, Lucas DO, Hartman AL, et al. How do you improve compliance? *Pediatrics*. 2005;115(6):e718-724.
52. Wu AW, Ammassari A, Antinori A. Adherence to antiretroviral therapy: where are we, and where do we go from here? *J Acquir Immune Defic Syndr*. 2002;31 Suppl 3:S95-97.
53. Simoni JM, Amico KR, Pearson CR, et al. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. *Curr Infect Dis Rep*. 2008;10(6):515-521.
54. Behforouz HL, Farmer PE, Mukherjee JS. From directly observed therapy to accompagnateurs: enhancing AIDS treatment outcomes in Haiti and in Boston. *Clin Infect Dis*. 2004;38 Suppl 5:S429-436.
55. Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. *J Acquir Immune Defic Syndr*. 2004;36(4):929-934.
56. Jayaweera DT, Kolber MA, Brill M, et al. Effectiveness and tolerability of a once-daily amprenavir/ritonavir-containing highly active antiretroviral therapy regimen in antiretroviral-naïve patients at risk for nonadherence: 48-week results after 24 weeks of directly observed therapy. *HIV Med*. 2004;5(5):364-370.
57. Williams AB, Fennie KP, Bova CA, et al. Home visits to improve adherence to highly active antiretroviral therapy: a randomized controlled trial. *J Acquir Immune Defic Syndr*. 2006;42(3):314-321.
58. Myung P, Pugatch D, Brady MF, et al. Directly observed highly active antiretroviral therapy for HIV-infected children in Cambodia. *Am J Public Health*. 2007;97(6):974-977.

59. Ford N, Nachega JB, Engel ME, et al. Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomised clinical trials. *Lancet*. 2009;374(9707):2064-2071.
60. Hart JE, Jeon CY, Ivers LC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. *J Acquir Immune Defic Syndr*. 2010;54(2):167-179.
61. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS*. 2009;23(10):803-807.
62. Boyle BA, Jayaweera D, Witt MD, et al. Randomization to once-daily stavudine extended release/lamivudine/efavirenz versus a more frequent regimen improves adherence while maintaining viral suppression. *HIV Clin Trials*. 2008;9(3):164-176.
63. Molina JM, Podsadecski TJ, Johnson MA, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. *AIDS Res Hum Retroviruses*. 2007;23(12):1505-1514.
64. Parienti JJ, Bangsberg DR, Verdon R, et al. Better adherence with once-daily antiretroviral regimens: a meta-analysis. *Clin Infect Dis*. 2009;48(4):484-488.
65. Campo RE, Cohen C, Grimm K, et al. Switch from protease inhibitor- to efavirenz-based antiretroviral therapy improves quality of life, treatment satisfaction and adherence with low rates of virological failure in virologically suppressed patients. *Int J STD AIDS*. 2010;21(3):166-171.
66. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader*. 2000;10(2):88-94.
67. DiIorio C, Resnicow K, McDonnell M, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a pilot study. *J Assoc Nurses AIDS Care*. 2003;14(2):52-62.
68. Hammami N, Nostlinger C, Hoeree T, et al. Integrating adherence to highly active antiretroviral therapy into children's daily lives: a qualitative study. *Pediatrics*. 2004;114(5):e591-597.
69. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics*. 2007;119(4):e893-899.
70. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics*. 2000;105(6):E80.
71. Berrien VM, Salazar JC, Reynolds E, et al. Adherence to antiretroviral therapy in HIV-infected pediatric patients improves with home-based intensive nursing intervention. *AIDS Patient Care STDS*. 2004;18(6):355-363.
72. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses*. 2010;26(9):947-953.
73. Tugenberg T, Ware NC, Wyatt MA. Paradoxical effects of clinician emphasis on adherence to combination antiretroviral therapy for HIV/AIDS. *AIDS Patient Care STDS*. 2006;20(4):269-274.
74. Wang X, Wu Z. Factors associated with adherence to antiretroviral therapy among HIV/AIDS patients in rural China. *AIDS*. 2007;21 Suppl 8:S149-155.
75. Molassiotis A, Morris K, Trueman I. The importance of the patient-clinician relationship in adherence to antiretroviral medication. *Int J Nurs Pract*. 2007;13(6):370-376.
76. Van Wingham J, Telfer B, Reid T, et al. Implementation of a comprehensive program including psycho-social and treatment literacy activities to improve adherence to HIV care and treatment for a pediatric population in Kenya. *BMC Pediatr*. 2008;8:52.